Avapritinib Decreased Symptom Burden in Patients With Indolent Systemic Mastocytosis in the Registrational Double-Blind, Placebo-Controlled PIONEER Study

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Matthew P. Giannetti,[1a*] Cem Akin,[2] Cristina Bulai Livideanu,[3] Vito Sabato,[4] Paul Van Daele,[5] Thanai Pongdee,[6] Stéphane Barete,[7] Peter Vadas,[8] Marcus Maurer,[9,10] Frank Siebenhaar,[9,10] Massimo Triggiani,[11] Patrizia Bonadonna,[12] Karin Hartmann,[13,14] Mar Guilarte,[15] Princess U. Ogbogu,[16] Caroline Gaudy-Marqueste,[17] Ilda Bidollari,[18] Teresa Green,[18] Hui-Min Lin,[18] Maria Roche,[18] Erin Sullivan,[18] Mariana Castells,[1] Hanneke Oude Elberink[19]

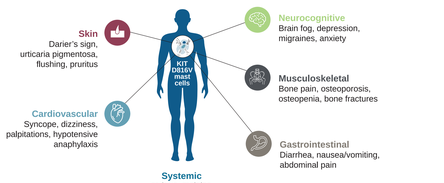
[1]Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [2]University of Michigan, Ann Arbor, MI, USA; [3]Département de Dermatologie, Centre de Référence des Mastocytoses (CEREMAST), Centre Hospitalier Universitaire de Toulouse, Toulouse, France; [4]Department of Immunology, Allergology and Rheumatology, University of Antwerp, and Antwerp University Hospital, Antwerp, Belgium; [5]Department of Internal Medicine, Erasmus Medical Center, Rotterdam, Netherlands; [6]Division of Allergic Diseases, Mayo Clinic, Rochester, MN, USA; [7]Unit of Dermatology CEREMAST AP-HP, Pitié-Salpêtrière Hospital, Sorbonne Université, Paris, France; [8]St Michael's Hospital, University of Toronto, Toronto, ON, Canada; [9]Institute of Allergology, Charité – Universitätsmedizin Berlin, Corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [10]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany; [11]University of Salerno, Salerno, Italy; [12]Unità Semplice Dipartimentale di Allergologia, Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy; [13]Division of Allergy, Department of Dermatology, University Hospital Basel and University of Basel, Basel, Switzerland; [14]Department of Biomedicine, University Hospital Basel and University of Basel, Basel, Switzerland; [15]Hospital Universitari Vall d'Hebron, Institut de Recerca (VHIR), Barcelona, Spain; [16]Division of Pediatric Allergy, Immunology and Rheumatology, Department of Pediatrics, University Hospitals Rainbow Babies and Children's Hospital, Case Western Reserve University School of Medicine, Cleveland, OH, USA; [17]Dermatology and Skin Cancer Department, Assistance Publique Hôpitaux de Marseille, Aix-Marseille University, Marseille, France; [18]Blueprint Medicines Corporation, Cambridge, MA, USA; [19]Department of Allergology, University Medical Center Groningen Research Institute Asthma and COPD, University of Groningen, Groningen, Netherlands

**Presenting author*

Introduction

- Indolent systemic mastocytosis (ISM) is a clonal mast cell disease driven by the *KIT* D816V mutation in ~95% of patients[1–3]
- Patients with ISM may experience life-long debilitating symptoms including life-threatening anaphylaxis and poor quality of life (QoL) with significant morbidity[4–8] (**Figure 1**)

Figure 1. ISM symptoms[4–8]



ISM, indolent systemic mastocytosis.

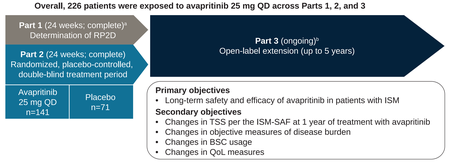
- Most patients with ISM rely on polypharmacy for the management of symptoms. However, in many patients, symptoms are not adequately controlled with best supportive care (BSC) medications[9–11]
- Avapritinib is a potent, oral tyrosine kinase inhibitor that selectively targets the KIT D816V mutation[12,13]
- In the PIONEER trial (NCT03731260), avapritinib plus BSC has been shown to improve symptoms, improve QoL, and reduce biomarkers of mast cell burden *versus* placebo plus BSC in patients with moderate to severe ISM[11]
  - Patients experienced an improvement in all ISM symptoms per the ISM Symptom Assessment Form (ISM-SAF®)[11]
- Avapritinib is approved in the USA and Europe for adult patients with ISM based on the outcomes of the PIONEER trial[12,13]
- Here we present updated longer-term findings on symptom burden in patients with ISM enrolled in PIONEER

[a]ISM-SAF © 2018 Blueprint Medicines Corporation.

Methods

- PIONEER, a global, randomized, double-blind, placebo-controlled trial, evaluated the safety, efficacy, and QoL in adult patients with ISM receiving avapritinib + BSC (avapritinib) compared with patients receiving placebo + BSC (placebo)
- Adult patients with centrally confirmed ISM with uncontrolled moderate to severe symptoms (total symptom score [TSS] of ≥28 at screening), despite treatment with ≥2 BSC, were eligible for the study
- Upon completion of Part 1 (the dose-finding portion) or Part 2 (the randomized, double-blind, placebo-controlled portion) of the PIONEER study, patients were eligible to receive open-label avapritinib for up to 5 years (Part 3, ongoing; **Figure 2**)
- The ISM-SAF is a validated symptom assessment tool specifically developed for evaluation of ISM symptomology[14–16] (**Figure 3**)
  - TSS is based on self-reported severity of 11 ISM symptoms
  - The ISM-SAF was developed over the past 8 years with input from patients, disease experts, and global regulatory agencies[16]
- The primary endpoint of PIONEER Part 2 was the mean change in ISM-SAF TSS from baseline to Week 24 in avapritinib-treated patients compared to placebo, and in Part 3 the primary endpoint is to assess the long-term efficacy and safety of avapritinib
- Part 2 data are presented at a cut-off of June 23, 2022, and Part 3 long-term extension data at a cut-off of April 7, 2023

Figure 2. PIONEER study design



[a]The recommended Part 2 dose of avapritinib was identified based on efficacy and safety results from Part 1 that included four blinded, randomized cohorts: 25 mg avapritinib (n=10), 50 mg avapritinib (n=10), 100 mg avapritinib (n=10), and placebo (n=9). [b]Part 3 includes 135 patients who received avapritinib in Part 2 and 66 patients who received placebo in Part 2, as well as patients from Part 1.
BSC, best supportive care; ISM-SAF, Indolent Systemic Mastocytosis Symptom Assessment Form; QD, once daily; QoL, quality of life; RP2D, recommended Part 2 dose; TSS, total symptom score.

Figure 3. The ISM-SAF is a validated symptom assessment tool[14–16]

ISM-SAF		
Domain	**ISM Symptom**	**Scoring**
Gastrointestinal	Abdominal pain Diarrhea Nausea	Scored 0–10 daily on handheld device 0 = no symptom 10 = **worst imaginable** symptom Analyzed as a 14-day moving average
Skin	Spots Itching Flushing	
Neurocognitive	Brain fog Headache Dizziness	
Systemic	Bone pain Fatigue	
TSS (0–110) **Higher score represents more severe symptoms**		

- The mean change in TSS (0–110) of ISM-SAF and the mean change in symptom domain scores (0–30) were measured

Table 1. Baseline characteristics

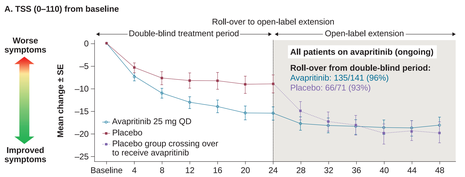
	Randomized-controlled Part 2	
Patient demographic	**Avapritinib 25 mg QD (n=141)**	**Placebo (n=71)**
Age (years), median (range)	50.0 (18–77)	54.0 (26–79)
Female, n (%)	100 (71)	54 (76)
ISM symptom burden		
TSS, mean (SD)	50.2 (19.1)	52.4 (19.8)
Most severe symptom score, mean (SD)	7.7 (1.7)	7.9 (1.7)
Mast cell burden		
Median serum tryptase (central), ng/mL (range)	38.4 (3.6–256.0)	43.7 (5.7–501.6)
Median bone marrow biopsy mast cells (central), % (range)	7.0 (1.0–50.0)	7.0 (1.0–70.0)
Mast cell aggregates present, n (%)	106 (75)	57 (80)
Median *KIT* D816V VAF in peripheral blood, % (range)[a]	0.4 (0.0–41.3)	0.3 (0.0–36.7)
KIT D816V positivity, n (%)	131 (93)	69 (97)
SM therapy		
Prior cytoreductive therapy, n (%)	19 (13)	7 (10)
Prior TKI therapy, n (%)	10 (7)	4 (6)
BSC use		
Number of BSC treatments, median (range)	3 (0–11)	4 (1–8)

[a]By digital droplet polymerase chain reaction; limit of detection 0.02%.
SD, standard deviation; SM, systemic mastocytosis; TKI, tyrosine kinase inhibitor; VAF, variant allele fraction.

Results

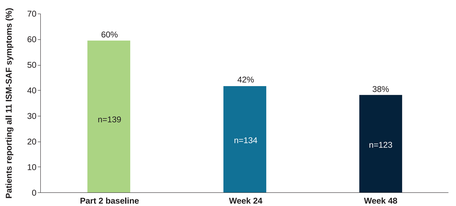
- In Part 2, baseline characteristics and demographics were balanced between avapritinib and placebo groups (**Table 1**)
- Avapritinib demonstrated a significant and durable improvement in symptoms *versus* placebo at Week 24, as shown by the decrease in TSS, maintained up to Week 48 (**Figure 4A**)
- In each symptom domain, all three individual symptoms (Gastrointestinal [abdominal pain, diarrhea, nausea], **Figure 4B**; Neurocognitive [brain fog, headache, dizziness], **Figure 4C**; Skin [spots, itching, flushing], **Figure 4D**) improved with avapritinib treatment at 24 and 48 weeks and contributed to the decrease in the domain symptom score

Figure 4. Mean change in ISM-SAF TSS and symptom domains over time[a]



[a]Only patients from Part 2 were included within the assessment.
SE, standard error.

Figure 5. Proportion of patients reporting all 11 ISM-SAF symptoms (avapritinib patients only)



- With avapritinib treatment, the number of patients who were reporting all 11 ISM-SAF symptoms at baseline (60%) reduced at Week 24 (42%) and further improved at Week 48 (38%) (**Figure 5**)

Placebo-controlled evaluation of safety

- Avapritinib 25 mg QD was generally well tolerated, with a similar safety profile to placebo during the blinded, randomized Part 2 (median follow-up of 5.5 months; **Table 2**)
- The majority of adverse events (AEs) were Grade 1 or 2 with a low rate of discontinuation
- Serious AEs (SAEs) were reported more frequently in the placebo group (no treatment-related SAEs in either group)
- Edema AEs were higher in the avapritinib group (majority Grade 1), and did not result in discontinuation
- AEs of special interest include intracranial hemorrhage (ICH) and cognitive effects. No ICHs were observed. The rate of cognitive effects in patients treated with avapritinib (3%) and placebo (4%) were similar

Longer-term open-label evaluation of safety

- The Part 3 open-label extension of PIONEER allowed for the assessment of longer-term safety of avapritinib at 25 mg QD in 226 patients (median follow-up of 18 months)
- No new safety concerns were observed with longer follow-up; the most common treatment-related AEs (TRAEs) (≥5% of patients) remained consistent to those reported during Part 2 (**Table 2**)
- No ICHs were observed. The rate of cognitive effects remained low

Table 2. Summary of AEs

	Randomized-controlled Part 2		All patients who received avapritinib 25 mg QD during Parts 1, 2, or 3 (n=226)[a]
	Avapritinib 25 mg QD (n=141)	**Placebo (n=71)**	
Any AEs, n (%)	128 (91)[b]	66 (93)[b]	223 (99)
Grade ≥3 AEs	30 (21)[b]	15 (21)[b]	86 (38)
Any grade TRAEs, n (%)	77 (55)	32 (45)	151 (67)
Grade ≥3 TRAEs	3 (2)	2 (3)	11 (5)
SAEs, n (%)	7 (5)	8 (11)	31 (14)
Most frequently reported TRAEs (≥5% of patients)			
Headache	11 (8)	7 (10)	20 (9)
Nausea	9 (6)	6 (8)	17 (8)
Peripheral edema	9 (6)	1 (1)	23 (10)
Periorbital edema	9 (6)	2 (3)	18 (8)
Dizziness	4 (3)	5 (7)	9 (4)
TRAEs leading to discontinuation	2 (1)	1 (1)	6 (3)

[a]This includes patients from Part 1 who continued avapritinib 25 mg QD or crossed over from placebo to avapritinib 25 mg QD. This also includes patients from Part 2 who received avapritinib 25 mg QD or who crossed over from placebo to avapritinib 25 mg QD. [b]AEs refer to treatment-emergent AEs, defined as any AE that occurred between day 1 of Part 2 through to a day prior to day 1 of Part 3 if the patient crossed over to Part 3; if the patient did not cross over, then through 30 days after the last dose of study drug.
AEs, adverse events; SAEs, serious adverse events; TRAEs, treatment-related AEs.

- The number of TRAEs leading to discontinuation remained low
- Drug interruptions were predominantly for non-TRAE and other reasons
  - For example, a 33-year-old male interrupted treatment to successfully father a pregnancy and then resumed avapritinib 190 days later

Conclusions

- Avapritinib-treated patients showed rapid and clinically meaningful improvements in disease-related symptoms compared with placebo-treated patients at 24 weeks of treatment
- Durable benefit was seen at 48 weeks of therapy, with continued symptom improvement seen across all three symptom domains (gastrointestinal, neurocognitive, and skin)
- Patients eliminated more symptoms on avapritinib *versus* placebo after 24 weeks of treatment, and this continued to improve at Week 48
- Avapritinib was generally well tolerated, with a similar safety profile to placebo and no new safety concerns observed after a median treatment duration of 18 months

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